

Thoughts on Scopes of Biological Models

September 18, 2015

Part I

The equations

I'm going to write here all the equations in both approaches, for reference. In this paper, I'll use the updated notation I used in the previous Email:

- in - a single cell.
- out - outside of all the cells.
- sum - all the cells together.
- tot - all the system/organism.

1 Previous Work

1.1 Sum Approach (this set of equations will be denoted using [Sum, I] from now on)

The equations Ido wrote are the following:

$$\frac{dA_{sum}}{dt} = -c_1 a a_{in} A_{sum} - c_2 A_{sum} + c_4 L A_{sum} \quad (1.1.1)$$

$$\frac{dL A_{sum}}{dt} = c_3 L_{in} \cdot A_{sum} - c_4 L A_{sum} + c_6 L A_{2,sum} \quad (1.1.2)$$

$$\frac{dL A_{2,sum}}{dt} = c_5 L A_{sum}^2 - c_6 L A_{2,sum} \quad (1.1.3)$$

$$d(a_0 + a_1) = 0 \quad (1.1.4)$$

$$\frac{da_1}{dt} = c_7 a_0 L A_{2,sum} - c_8 a_1 \quad (1.1.5)$$

$$\frac{dTRLV_{sum}}{dt} = A_{RBS} \cdot (a_0 v_0 + a_1 v_1) - c_9 TRLV_{sum} \quad (1.1.6)$$

$$d(b_0 + b_1) = 0 \quad (1.1.7)$$

$$\frac{db_1}{dt} = c_1 b_0 TRLV_{sum} - c_{11} b_1 \quad (1.1.8)$$

$$\frac{dccb_{sum}}{dt} = B_{RBS} \cdot (b_0 u_0 + b_1 u_1) - c_{12} cccb_{sum} \quad (1.1.9)$$

$$\frac{dx_{sum}}{dt} = c_{13} N(t) \quad (1.1.10)$$

$$\frac{dL_{in}}{dt} = c_{14} - c_{15} L_{in} + \frac{c_4 L A_{sum}}{N(t)} \quad (1.1.11)$$

$$L_{sum} = N(t) L_{in} \quad (1.1.12)$$

$$\frac{daa_{in}}{dt} = c_{16} - c_{17} aa_{in} \quad (1.1.13)$$

$$aa_{sum} = N(t) aa_{in} \quad (1.1.14)$$

$$\frac{dN(t)}{dt} = N(t) \left(1 - \frac{N(t)}{N_{max}}\right) \quad (1.1.15)$$

They are pretty outdated. I'll update and correct them on section 2.

1.2 In Approach [In, I]

The most updated equations we've derived for this approach are the following:

$$\frac{dA_{in}}{dt} = -c_1 aa_{in} A_{in} - c_2 A_{in} + c_4 L A_{in} - (c_3 L_{in} \cdot A_{in}) \quad (1.2.1)$$

$$\frac{dL A_{in}}{dt} = c_3 L_{in} \cdot A_{in} - c_4 L A_{in} - 2(c_5 L A_{in}^2 - c_6 L A_{2,in}) \quad (1.2.2)$$

$$\frac{dL A_{2,out}}{dt} = c_5 L A_{in}^2 - c_6 L A_{2,in} - (c_7 a_0 L A_{2,in} - c_8 a_1) \quad (1.2.3)$$

$$\frac{da_{0,in}}{dt} = -\frac{da_{1,in}}{dt} \quad (1.2.4)$$

$$\frac{da_{1,in}}{dt} = c_7 a_{0,in} L A_{2,in} - c_8 a_{1,in} \quad (1.2.5)$$

$$\frac{dTRLV_{in}}{dt} = A_{RBS} \cdot (a_{0,in} v_0 + a_{1,in} v_1) - c_9 TRLV_{in} - (c_{10} b_{0,in} TRLV_{in} - c_{11} b_{1,in}) \quad (1.2.6)$$

$$\frac{db_{0,in}}{dt} = -\frac{db_{1,in}}{dt} \quad (1.2.7)$$

$$\frac{db_{1,in}}{dt} = c_{10} b_{0,in} TRLV_{in} - c_{11} b_{1,in} \quad (1.2.8)$$

$$\frac{dccb_{in}}{dt} = B_{RBS} \cdot (b_{0,in}u_0 + b_{1,in}u_1) - c_{12}ccb_{in} \quad (1.2.9)$$

$$\frac{dx_{tot}}{dt} = c_{13}N(t) \quad (1.2.10)$$

$$\frac{dL_{in}}{dt} = c_{14} - c_{15}L_{in} \quad (1.2.11)$$

$$\text{-----} \quad (1.2.12)$$

$$\frac{daa_{in}}{dt} = c_{16} - c_{17}aa_{in} \quad (1.2.13)$$

$$\text{-----} \quad (1.2.14)$$

$$\frac{dN(t)}{dt} = N(t)(1 - \frac{N(t)}{N_{max}}) \quad (1.2.15)$$

In the following section I'll update these equations a bit. As for Michaelis Menten Kinetics, they aren't critical for now. I'll leave it for the time being

2 Equations updating

[In 1]'s equations aren't describing our system very well for two reasons: they don't contain our recent advances (which are marked here) and we didn't understand what we're doing when we wrote them. I'll address the second reason first.

2.1 Wrong Using of Scales

Let's take a look at [sum I, eq.3].

$$\frac{dLA_{2,sum}}{dt} = c_5LA_{sum}^2 - c_6LA_{2,sum}$$

The term $c_5LA_{sum}^2$ describes the rate of $LA_{2,sum}$ forming, and uses 'Law of Mass Action' for this. What 'Law of Mass Action' says? It says that reaction rate is proportional to the product of its reactants. However, you can't use it blindly. Let's take a look at the following situations: 1. We have 1000 cells and in all of them together there are 100,000 molecules of LA, ie. $LA_{sum} = 100,000$. 2. We put 100,000 molecules in a test tube (with same volume as the total volume of the cells). In both cases the term $c_5LA_{sum}^2$ describes the reaction rate, but the two situations are different. We used mass action law between all the molecules in the system and themselves, but we can't do it. The term we've got is based on the assumption that *every* LA molecule (which is counted in 'sum') can meet *every other* molecule (which is counted in 'sum'), but they can't as most of these molecules are in a different cell. The correct term is $c_5LA_{sum}LA_{in}$. You can try to find an explanation to it using words like we did

when we derived these equations and has led us to wrong ones (like, 'lets take a look at a single LA, it has a chance to react of $c_5 LA_{in}$ so sum over all LA molecules in all the cells...), but the real reason for its being the correct term is the fact: $c_5 LA_{sum} LA_{in} = N \cdot (c_5 LA_{in} LA_{in})$. This kind of connection between sum reaction rate and in reaction rate holds for *all* the reactions. That's because what we do when we describe the system using 'sum' is to multiply what happens in a single cell by N. It's not matter of better accuracy, the former equations ([Sum I]) were just wrong. I'll generalise my statement here: let's note the reaction rate of a reaction in 'sum' scale with $F_{sum}()$ and in '*in*' scale with $F_{in}()$. I claim that always $F_{sum}() = N \cdot F_{in}()$. I've explained my reasoning in the emails so I'm not going to do it again here.

I'll write here all the other patch-needed equations and their corrected form. The scale of $a_{0/1}$ and $b_{0/1}$ isn't mentioned in Ido's equations, so I'll try to follow the pattern from the other equations with it.

[Sum I, eq.3]:

$$\frac{dLA_{2,sum}}{dt} = c_5 LA_{sum} LA_{in} - c_6 LA_{2,sum}$$

[Sum I, eq.4]:

$$d(a_{0,in} + a_{1,in}) = 0$$

[Sum I, eq.5]: (Right now I'm guessing that the a's should be '*sum*'. It's up to discussion)

$$\frac{da_{1,sum}}{dt} = c_7 a_{0,in} LA_{2,sum} - c_8 a_{1,sum}$$

[Sum I, eq.6]:

$$\frac{dTRLV_{sum}}{dt} = A_{RBS} \cdot (a_{0,sum} v_0 + a_{1,sum} v_1) - c_9 TRLV_{sum}$$

[Sum I, eq.7]:

$$d(b_{0,in} + b_{1,in}) = 0$$

[Sum I, eq.8]: (Right now I'm guessing that the b's should be '*sum*'. It's up to discussion)

$$\frac{db_1}{dt} = c_1 b_{0,in} TRLV_{sum} - c_{11} b_{1,in}$$

[Sum I, eq.9]:

$$\frac{dccb_{sum}}{dt} = B_{RBS} \cdot (b_{0,sum} u_0 + b_{1,sum} u_1) - c_{12} cccb_{sum}$$

[Sum I, eq.10]: (this isn't a significant change, I just replaced '*sum*' with '*tot*')

$$\frac{dx_{tot}}{dt} = c_{13} N(t)$$

[Sum I, eq.11]: I have not even the slightest idea why we have wrote this equation using '*in*'. Its production acts exactly the same way the rest of the materials do. I think that when chose to use here '*in*' we didn't understand its meaning thoroughly. When I discuss the difference between the approaches later I hope it'll become more apparent.

$$\frac{dL_{sum}}{dt} = c_{14}N(t) - c_{15}L_{sum} + c_4LA_{sum}$$

[Sum I, eq.13]: Same note as in eq.11.

$$\frac{daa_{in}}{dt} = c_{16} - c_{17}aa_{in}$$

2.2 Recent Advances

Without much ado, I'll write here all the updated equations for 'sum'. I'll omit eq.12 and 14 because there are now much more mentions of '*in*' scale amounts. Remember that for any material Y, $Y_{sum} = Y_{in}N(t)$ holds. The following equations will be denoted as [Sum II].

$$\frac{dA_{sum}}{dt} = -c_1aa_{in}A_{sum} - c_2A_{sum} + c_4LA_{sum} - (c_3L_{in} \cdot A_{sum}) \quad (2.2.1)$$

$$\frac{dLA_{sum}}{dt} = c_3L_{in} \cdot A_{sum} - c_4LA_{sum} + c_6LA_{2,sum} - 2(c_5LA_{sum}LA_{in} - c_6LA_{2,sum}) \quad (2.2.2)$$

$$\frac{dLA_{2,sum}}{dt} = c_5LA_{sum}LA_{in} - c_6LA_{2,sum} - (c_7a_{0,in}LA_{2,sum} - c_8a_{1,sum}) \quad (2.2.3)$$

$$\frac{d(a_{0,in} + a_{1,in})}{dt} = 0 \quad (2.2.4)$$

$$\frac{da_{1,sum}}{dt} = c_7a_{0,in}LA_{2,sum} - c_8a_{1,sum} \quad (2.2.5)$$

$$\frac{dTRLV_{sum}}{dt} = A_{RBS} \cdot (a_{0,sum}v_0 + a_{1,sum}v_1) - c_9TRLV_{sum} - (c_1b_{0,in}TRLV_{sum} - c_{11}b_{1,in}) \quad (2.2.6)$$

$$\frac{d(b_{0,in} + b_{1,in})}{dt} = 0 \quad (2.2.7)$$

$$\frac{db_1}{dt} = c_1b_{0,in}TRLV_{sum} - c_{11}b_{1,in} \quad (2.2.8)$$

$$\frac{dccb_{sum}}{dt} = B_{RBS} \cdot (b_{0,sum}u_0 + b_{1,sum}u_1) - c_{12}ccb_{sum} \quad (2.2.9)$$

$$\frac{dx_{tot}}{dt} = c_{13}N(t) \quad (2.2.10)$$

$$\frac{dL_{sum}}{dt} = c_{14}N(t) - c_{15}L_{sum} - (c_3L_{in} \cdot A_{sum} - c_4LA_{sum}) \quad (2.2.11)$$

$$----- \quad (2.2.12)$$

$$\frac{daa_{sum}}{dt} = c_{16}N(t) - c_{17}aa_{sum} \quad (2.2.13)$$

$$----- \quad (2.2.14)$$

$$\frac{dN(t)}{dt} = N(t)(1 - \frac{N(t)}{N_{max}}) \quad (2.2.15)$$

As for [In I], I'll do only one change: Our current equation for $\frac{dL_{in}}{dt}$, [In I, eq.11]

$$\frac{dL_{in}}{dt} = c_{14} - c_{15}L_{in}$$

lacks a term for formation and dissociation of LA complexes. ~~We don't understand the system enough to omit it~~ We can't omit it because omitting it is actually omitting the reduction in the amount of L that happens as LA forms. This assumption is equivalent to assuming L is a a foundation that never runs dry, that no matter how much L we take for forming LA, L won't reduce. This is wrong, so I'll put the term back. Our new equation in this approach will be:

$$\frac{dL_{in}}{dt} = c_{14} - c_{15}L_{in} - (c_3L_{in} \cdot A_{in} - c_4LA_{in})$$

The equation system with it will be denoted with [In II]. It also explains [Sum II, 11] which is denoted with (*).

Part II

Analysis

3 Simplified Model

So, After we have consistent equations for both approaches, let's think what they mean and what is the difference between them. We are going to take a look at a simplified problem: a system with a single equation . Using the notation that was introduced at section 2.1, we can write:

In 'in' scale:

$$\frac{dY_{in}}{dt} = f_{in}() \quad (3.0.16)$$

In '*sum*' scale:

$$\frac{dY_{out}}{dt} = f_{out}() \quad (3.0.17)$$

When $f_{in}()$ describes rate of one reaction or more and maybe involve some other materials, it doesn't matter, in the scale of single cell. $f_{sum}()$ is the equivalent for '*sum*'. This system is very much the same as our in regards to *in* /*sum* dispute (Yes! That's the new name of the dispute). It's not really simplified: it just means that we are going to focus at a single material at a time. We are going to see now what is the difference between the situations equations 3.1.1 and 3.1.2 describe. We know that:

$$f_{sum}() = N \cdot f_{in}()$$

$$Y_{sum} = N \cdot Y_{in}$$

So 3.1.2 become:

$$\frac{d(N \cdot Y_{in})}{dt} = N \cdot f_{in}() \quad (3.0.18)$$

You might feel an urge to cancel N on both sides and get that '*sum*' equation is equivalent to '*in*' equation, but N isn't a constant so we get:

$$N \frac{dY_{in}}{dt} + \frac{dN}{dt} \cdot Y_{in} = N \cdot f_{in}() \quad (3.0.19)$$

Note that we can't substitute $\frac{dY_{in}}{dt} = f_{in}()$ into this equation because 3.1.1 holds only in the '*in*' scale. Doing so would be in fact assuming that the amounts in '*in*' scale are the same as in '*sum*' scale, and that's what we want to check out.

Without falling to this trap, let's examine the result. By dividing by N(t) we get:

$$\frac{dY_{in}}{dt} = f_{in}() - \frac{\dot{N}}{N} \cdot Y_{in} \quad (3.0.20)$$

That's different from what we've got at '*in*' scale, so we do get different results when we use '*sum*' instead of '*in*' and I was wrong when I claimed otherwise in the emails. However, the question is what we do with it. We could shrug it off as a miraculous enhanced accuracy and use it in our model (that's exactly what we have done until now, in my opinion. Not that my hands are clean about it), but I'm going to try to understand what it's mean and what makes the difference.

4 The Mysterious Term

Let's take eq. 3.1.4 (Equation number pie!) and as physicists custom goes, multiply it by dt . We get

$$NdY_{in} + dN \cdot Y_{in} = N \cdot f_{in}() \cdot dt \quad (4.0.21)$$

$N \cdot f_{in}() \cdot dt$ is the amount of produced Y in all the cells together during the short interval dt . NdY_{in} is the change in the amount of Y during this interval in all the existing cells together, so we get:

$$[amount\ changed\ in\ all\ the\ cells\ during\ dt] = [produced\ in\ all\ the\ cells\ during\ dt] - dN \cdot Y_{in} \quad (4.0.22)$$

So what does the mysterious term $dN \cdot Y_{in}$ mean? First, I think it's obvious this term has nothing to do with stochastic process inside the cell so for the very least, this approach doesn't achieve its declared goal. I thought it over for some time and came to a conclusion: this term represents the following hypothetical process: when a new cell is created, an amount of Y_{in} moves from the existing cells into the new one. We haven't payed heed for the change in the number of cells in our model yet. It's never too late to do so.

5 Population Growth

When a cell gets divided, its cytoplasm is divided between its offspring. We shall assume the time of the binary fission is small enough no to affect the processes we describe. Before the binary fission, the cell doesn't work overtime to assure its offspring will have enough LA, but I believe it does replicate its plasmid so the amount of the strands is constant all time. So, provided we have a closed system of single cell, on cell replication the amount of all the materials is divided between it's offspring and preserved in the system, apparent from the amount of $a_{0/1}, b_{0/1}$ which is doubled. So what does it mean for the equations? That when a new cell is created in our simplified system, it doesn't affect Y_{sum} 's amount (provided it's a regular material, not a strand), but it does affect Y_{in} amount because the average amount in each cell decreases as the number of cells increase. Let's think how it's expressed in each model. The previous argument seems to be in favour of the 'sum' approach. I, at least, were puzzled at this point as I couldn't understand what can be its vulnerability. Therefore, I conducted a theoretical experiment.

6 Theoretical Experiment

Imagine that, in our simplified system, Y isn't produced at all. That's mean, $f_{sum}() = f_{in}() = 0$. When we begin our observation, though, there is Y_0 of the material in each cell and the cells populate. I know this situation isn't

very probable (how you are going to put this Y_0 in?), but this is a theoretical experiment. I believe it's reasonable to assume that our method of describing biological system should work for this system. I mean, imagine that we take our regular system and freeze it at some point, preventing production of new materials but the cells still reproduce slowly or alternatively, they reproduce so fast so the production of the material Y is comparably slow (I'm not going to define it). You would not want all the mathematics to collapse at this case, right? Let's see what happens in each method of describing the experiment, using '*in*' and '*sum*'. Remember that our goal is to compute $Y_{sum}(t_1)$ for a certain $t_0 < t_1$ (which is equivalent, for example, to $X_{tot}(t_\infty)$ in our main system).

6.1 '*sum*'

Our problem is described in this approach using the following equation:

$$\frac{d(Y_{sum})}{dt} = f_{out}() = 0 \quad (6.1.1)$$

$$Y_{sum}(t_0) = Y_0 \cdot N(t_0) \quad (6.1.2)$$

and we want to compute $Y_{sum}(t_1)$. From eq. 3.4.1 it follows that Y_{sum} is constant, so $Y_{sum}(t_1) = Y_0 N_0$.

6.2 '*in*'

Our problem is described in this method/approach using the following equation:

$$\frac{d(Y_{in})}{dt} = f_{in}() = 0 \quad (6.2.1)$$

$$Y_{in}(t_0) = Y_0 \quad (6.2.2)$$

and we want to compute $Y_{sum}(t_1) = N(t_1)Y_{in}(t_1)$. From eq. 3.4.1 it follows that Y_{in} is constant, so $Y_{in}(t_1) = Y_{in}(t_0) = Y_0$. We get $Y_{sum}(t_1) = Y_0 N(t_1)$. Yeah.

6.3 Discussion

What we have got? in the '*in*' approach the amount of Y at the end of the experiment is proportional to the number of cells. The more cells you have, the more Y you get at the end. But it's not true in reality! There is no producing of Y in the system *at all*. No Y is produced, so it's total amount in the system can't increase. On the other hand, in '*sum*' approach we get that the total amount of Y is conserved, as it should be. That shows that the '*in*' approach isn't correct here, but it still doesn't mean the '*sum*' is correct. Let's analyse the problem in the '*in*' approach. The following argument holds for any of our

systems, not only in the theoretical experiment. In the '*in*' approach we have a precise description of what happens in a single living cell, no matter in which cell cycle's phase the cell is, as function of time passed from it's creation. There are no workarounds here. The problem is when we use it to compute the total amount of '*Y*' at the moment t_1 . To do it, we just multiply the amount that one cell produce at time span of t_1 with the number of cells existing at the end, and we derived it under the assumption that all the cells are equal. But they are not! Cells that have been created later will 'work' for shorter time span so they will produce less material by the time of t_1 . I'll describe the whole system here: On the beginning there are N_0 cells, which are going to live for t_1 second and produce $L_{in}(t_1)$ during the experiment. As the experiment goes on, more and more cells are created with reproduction. Each new cell inherits portion of its parent's materials, and let's consider two options: the proportions between the materials in the offspring are the same as in its parent so all the processes regarding cell destruction continue from the point they stopped before the binary fission. That's mean, the new cells will die from ccdb poisoning at the same moment as the older ones. This option assumes homogeneity in the distribution of the materials in the cell, or at least it's accurate 'on avarage' (please don't suggest here that using '*sum*' will solve the inaccuracy. I still stand behind my claim that '*sum*' isn't going to miraculously cancel randomness and I hope I've managed to persuade you about it). The other option is to assume something else, like that when we apply our remedy the cells have already reproduced as much as they could so we don't have to worry about cell growth. This assumption would simplify our model a lot, but I'm not going to do it here because it makes the '*in*'/'*sum*' dispute boring and I don't know whether it's a good assumption. So, back to our business. Let's look at a cell which is created at the moment t_2 . The cell will die with the others, but will live only and 'work' only $t_1 - t_2$ second. I'm not entirely sure whether even when we assume homogeneity all the cells will together, but I afraid it's still too complicated to take into account the diversity in cell's development. For instance, in our complete system in order to compute the total amount of enzyme X that have produced, we need to assume that across all the living cells, the X is produce at equal rate. It's not necessarily correct, as in a new cell there is less X so it decays slower. Therefore, this system is very complicated and hard to predict. The '*sum*' scale doesn't take into account the diversity in the amount of the materials between new cells and old one. So what is the difference between '*in*' and '*sum*', you may ask. The difference is that '*in*' describes: "When a new cell is created, an amount of materials, the same as the amount in the rest of the cells, appears magically at the new cell" or "When a cell reproduce, an exact copy appears magically beside him, with the same amounts of materials and all", while '*sum*' describes the following situation: "When a new cell created, immediately materials flow from the rest of the cells to the new one so all the cells will have a mutual amount of each materials." Think of few cups in of water in a row that are connected so water can flow freely between them. When you connect a new cup to the group, water from the rest will flow to the new one until the water levels will be equal. That's what the '*sum*' approach is based

on, in contrasting to '*in*' which is somewhat equivalent here to saying that the new cup will get to the water level of the rest without taking water from the other cups. The '*sum*' approach is clearly better here, but isn't ideal either. This analog isn't complete, as in reality, matter doesn't flow freely between cells. Immediately after a new cell is created, it has less materials then the rest so it acts differently from them. In the '*sum*' approach, the new cell lowers the average which is taken for updating of '*sum*', so less materials produced according to the equations. Hence, the '*sum*' approach apparently gives better estimation of the result but isn't accurate either, as it's correct only on average.

7 Conclusion

I think we should take '*in*' for the strands and '*sum*' for the rest. I want to stress that the reason I think we should favour '*sum*' for most of the materials is neither because it cancels random processes in the cells nor because our way of describing the processes at the scale of '*sum*' is more accurate, nor because it saves us from assuming uniformity. It's just because in '*in*' as cell is created, an adequate amount of materials appears in it (which is correct only in strands), and in '*sum*' materials that are equivalent to one cell's contents are reduced from the average amounts, in order to account for to the 2 new cells that share now the contents of their parent. When I write it here, neither of the options sound very good. I'd be glad to hear your thoughts. I'd also be glad if you consider the ultimate solution.

8 Ultimate Solution

We can take the number of the cells to be constant (or almost constant), take '*in*' everywhere, and forget all this hustle.

9 Alternative Solution

Suggested equations, with some Menten Michaelis for good measure:

$$\frac{dA_{sum}}{dt} = -\frac{c_1 a a_{in} A_{sum}}{c_{18} + A_{sum}} - c_2 A_{sum} + c_4 L A_{sum} - (c_3 L_{in} \cdot A_{sum}) \quad (9.0.1)$$

$$\frac{dL A_{sum}}{dt} = c_3 L_{in} \cdot A_{sum} - c_4 L A_{sum} - 2(c_5 L A_{sum} L A_{in} - c_6 L A_{2,sum}) \quad (9.0.2)$$

$$\frac{dL A_{2,sum}}{dt} = c_5 L A_{sum} L A_{in} - c_6 L A_{2,sum} - (c_7 a_{0,in} L A_{2,sum} - c_8 a_{1,sum}) \quad (9.0.3)$$

$$\frac{d(a_{0,in} + a_{1,in})}{dt} = 0 \quad (9.0.4)$$

$$\frac{da_{1,in}}{dt} = c_7 a_{0,in} L A_{2,in} - c_8 a_{1,in} \quad (9.0.5)$$

$$\frac{dTRLV_{sum}}{dt} = A_{RBS} \cdot (a_{0,sum} v_0 + a_{1,sum} v_1) - c_9 TRLV_{sum} - (c_1 b_{0,in} TRLV_{sum} - c_{11} b_{1,in}) \quad (9.0.6)$$

$$\frac{d(b_{0,in} + b_{1,in})}{dt} = 0 \quad (9.0.7)$$

$$\frac{db_{1,in}}{dt} = c_1 b_{0,in} TRLV_{in} - c_{11} b_{1,in} \quad (9.0.8)$$

$$\frac{dccb_{sum}}{dt} = B_{RBS} \cdot (b_{0,sum} u_0 + b_{1,sum} u_1) - c_{12} ccb_{sum} \quad (9.0.9)$$

$$\frac{dx_{tot}}{dt} = c_{13} N(t) \quad (9.0.10)$$

$$\frac{dL_{sum}}{dt} = c_{14} N(t) - c_{15} L_{sum} - (c_3 L_{in} \cdot A_{sum} - c_4 L A_{sum}) \quad (9.0.11)$$

$$----- \quad (9.0.12)$$

$$\frac{daa_{sum}}{dt} = c_{16} N(t) - c_{17} aa_{sum} \quad (9.0.13)$$

$$----- \quad (9.0.14)$$

$$\frac{dN(t)}{dt} = N(t) \left(1 - \frac{N(t)}{N_{max}}\right) \quad (9.0.15)$$

Done.